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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,094	10/22/2003	John H. Griffin	P-144-US2	4781

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EXAMINER	
COPPINS, JANET L	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 08/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/691,094	GRIFFIN ET AL.	
	Examiner	Art Unit	
	Janet L. Coppins	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-24,26-30,32 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-24,26-30,32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.D.

DETAILED ACTION

Claims 22-24, 26-30, 32, and 33 pending in the instant application.

Response to Amendment

1. Receipt is acknowledged of Applicants' Amendment, filed May 6, 2005. Accordingly, claims 25 and 31 have been cancelled, and claims 22, 26, 28, 28, and 32 have been amended.

Information Disclosure Statements

2. Receipt is acknowledged of Applicants' Informational Disclosure Statement (IDS), filed May 6, 2005, which has been considered by the Examiner. Please refer to Applicants' copy of the PTO-1449 form submitted herewith.

Claim Rejections - 35 USC § 112

3. The Examiner had previously rejected claims 22-33 under 35 USC 112, first paragraph, as not being enabled. Applicants contend in page 6 of the Response that, "The present specification provides an enabling disclosure of the processes of preparing and administering a compound of formula (Ia) or a composition comprising such a compound." Applicants also argue that the Examiner's analysis is directed towards utility rather than enablement, and that "...the specification together with the state of the art at the time the application was filed fully supports the breadth of the claims now presented." Applicants further point out the correlation between receptor tyrosine kinases and proliferative disorders, and the ability of receptor tyrosine kinases to inhibit the growth of certain types of tumors.

The Examiner respectfully disagrees, and maintains the enablement rejections to pending claims 22-24, 26-30, 32, and 33.

4. Regarding claims 22-24 and 28-30, the applicable rule is that "Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description," see MPEP 2163(II)(1), citing *In re Morris*, 127 F.3d 1048, 1053-1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). Applying the above rule to claims 22-24 and 28-30, the scope of the claimed invention would be a method of treating a condition responsive to any tyrosine kinase inhibitor, which at the time of this invention would have included at least 90 different types of tyrosine kinases in humans alone (as identified by tyrosine kinase genes in the human genome), of which 58 types were identified as being receptor type" tyrosine kinases, grouped into 20 "families," and the other 32 types were identified as "non-receptor" type tyrosine kinases, grouped into 10 "families." See Robinson, D., et al., "The protein tyrosine kinase family of the human genome," Oncogene, vol. 19, pp. 5548- 5557 (2000), at the abstract; at p. 5548, col. 2, lines 42 - 50, and at p. 5549, Table 1 (showing the 30 "families" of tyrosine kinases). Types of tyrosine kinase that are the focus of the claimed invention are PDGFR, c-Kit, VEGFR, and Flt-3.

Applying the rule from Morris to Claims 22 and 28, the broadest reasonable interpretation of the claims would encompass a method for inhibiting any type of tyrosine kinase, which, as noted in the Robinson reference above, includes at least 90 different types of tyrosine kinases, which could be divided into 30 "families" of "receptor" type and "non-receptor" type tyrosine kinases. According to the Specification, the scope of human diseases that would be affected by inhibition of tyrosine kinase would include many types of cancer (see Specification at p. 9), as well as cardiovascular diseases such as restenosis.

As noted below, the Specification provides *in vitro* data to demonstrate that compounds of the claimed invention could be used to inhibit tyrosine kinase in certain AML cells where the

receptor tyrosine kinases "Flt-3, VEGFR, and PDGFR" were known to be present. However, there were no working examples provided in the Specification where compounds of Formula (1) were actually administered, *in vivo*, to a mammal as a method of inhibiting tyrosine kinase, as claimed.

Given the references cited by Applicants (using VEGF-receptor inhibitors), the known art at the time, the high skill level of practitioners of the art, along with the *in vitro* data for the claimed invention and information about preferred dose and route of administration, a person of skill in the art would not require an undue quantity of experimentation to be enabled to use the claimed invention as "a method for inhibiting tyrosine kinase" for certain specific types of cancer, specifically breast cancer, prostate cancer, lung cancer, and pancreatic cancer. On the other hand, the disclosure does not provide sufficient data for the claimed invention to be used by the skilled artisan as "a tyrosine kinase inhibitor" or as a "method for inhibiting tyrosine kinases," without an undue quantity of experimentation, when those limitations are given their full range of interpretation beyond the scope of "AML, small cell lung cancer, prostate cancer, gastrointestinal cancer, breast cancer, brain cancer, and restenosis" to include any of the 30 "families" of tyrosine kinases listed in the Robinson reference, above.

However, beyond those six types of cancer, based on the analysis above, the disclosure does not enable the skilled practitioner to use the claimed compounds as inhibitors of tyrosine kinases, wherein that term is interpreted to include any of the other "families" of tyrosine kinases beyond the receptor tyrosine kinases disclosed in the Specification, or the diseases associated with them. To obviate the rejections brought under 35 U.S.C. 112, lst paragraph, it is suggested that: Claims 22, 26, and 27 be combined into a single claim (as well as combining claims 28, 32,

and 33), incorporating the enabled portions of the individual claims; for example, "A method for inhibiting tyrosine kinase for treating cancer selected from the group consisting of AML, small cell lung cancer, prostate cancer, gastrointestinal cancer, breast cancer, brain cancer, and restenosis, which comprises administering an effective amount of the compound as defined in claim 22 or a salt thereof to a patient in need of such treatment."

5. Regarding "cancer" and "solid tumor" in claims 26, 27, 32, and 33, the applicable rule is that each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description," see MPEP 2163(II)(1), citing *In re Morris*, 127 F.3d 1048, 1053-1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). Applying this rule to the above claims, the scope of diseases claimed to be treated would thereby include all types and kinds of cancer, including such diverse types of cancer as leukemia, breast cancer, prostate cancer, lung cancer and brain cancer. However, the Specification only describes two *in vitro* studies in human AML cells demonstrating concentrations of the claimed compounds of Formula (1) needed to suppress 50% of phosphorylation of Flt-3, VEGFR, and PDGFR (types of receptor tyrosine kinases) and 50% suppression of cell proliferation using MTT. (Specification at p. 25-28). Given the scope of the many types of cancer included within the claims, their varied etiologies, and the diversity of their patient populations, the disclosure in the Specification is insufficient to permit a person skilled in the art to practice the method for treating cancer ". . . by administering to a patient in need of treatment a therapeutically effective amount of a compound of formula (Ia)...." However, as described below, the Specification discloses sufficient support to enable treating certain specific types of cancer.

The text of claims 26 and 32 does not specify or enumerate those many types of cancer

that would fall within its scope, nor does the text specify the type of "solid tumor" in claims 27 and 33. As noted earlier, the applicable rule is that "Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." MPEP 2163(II)(1), citing *In re Morris*, 127 F.3d 1048, 1053-1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, claims 26, 27, 32, and 33 may be reasonably interpreted to encompass all forms of cancer, as neither the claims themselves nor the Specification expressly define a closed set of illnesses defined as "cancer." Specifically, claims 26, 27, 32, and 33 state only that the compounds are administered for treating cancer." On page 9, the Specification discloses the range of cancers encompassed by the present invention," ... such as forms of cancer which include, but are not limited to acute myeloid leukemia, small cell lung cancer, prostate cancer, gastrointestinal cancer, breast cancer and brain cancer, and other proliferative disorders, such as restenosis. The compounds may also be useful in restricting the "growth of solid tumors," and therefore claims 26, 27, 32, and 33 encompass an open-ended set of types of cancers or tumors. The scope of said claims reasonably encompasses such a broad spectrum of types of cancer that it is unreasonable to believe, on its face, that a particular chemical compound could be used to treat cancer of so many different types, in the absence of supporting scientific data or references in the disclosure to the contrary. Claim 27 and 33 incorporate the limitations of claims 22 and 28, but limit the types of cancer to six general types: AML, small cell lung cancer, prostate cancer, gastrointestinal cancer, breast cancer, brain cancer, and then fail to limit the "growth of a solid tumor."

6. At the time of this application, the tyrosine kinase pathway had been identified as one of the five main molecular pathways as targets for drug development for metastatic breast cancer.

See Awada, A., et al., "The pipeline of new anticancer agents for breast cancer treatment in 2003," Critical Reviews in Oncology/Hematology, vol. 48, pp. 45 - 63 at p. 46, 2nd column, line 3 (the five main targets were: (1) the tyrosine kinase signal transduction pathway, (2) the estrogen receptor pathway, (3) the cell cycle regulation pathway, (4) the apoptosis pathway, and (5) the angiogenesis pathway). At the time of the application the first of the humanized monoclonal antibodies targeting tyrosine kinase, called "trastuzumab," had been approved for use in the U.S. for treatment since September of 1998 for HER-2 positive metastatic breast cancer (other monoclonal antibodies, such as rituximab, were also approved for use in patients with non-Hodgkin's lymphoma but did not target HER-2). Of the "small molecule" chemical compounds designed as tyrosine kinase inhibitors (i.e., not monoclonal antibodies), the most advanced in development were the compounds "ZD-l839" (gefitinib) and "OSl-774" (erlotinib), which were in Phase I/II/III investigational studies at that time. (ZD-1839 was subsequently approved for use in non-small cell lung cancer patients in May of 2003 under the FDA'S accelerated approval process). Id. at p. 53, 2nd col, lines 5 - 28 and on p. 53, Table 5; see also Nahta, R., et al., "Novel pharmacological approaches in the treatment of breast cancer," Expert Opin. Investigational Drugs, vol. 12(6), pp. 909-921, especially at p. 913, 1st column, line 51 to p. 914, 2nd col., line 14 ("Tyrosine kinase inhibitors").

Tyrosine kinase inhibitors had also been tested in early-phase clinical studies in breast cancer, non-small cell lung cancer and prostate cancer, although they were not always shown to be effective, as one early-stage clinical trial of a tyrosine kinase inhibitor named "geftitinib" did not show any change in disease status in breast cancer patients. Nahta R., et al., "Growth Factor Receptors in Breast Cancer: Potential for Therapeutic Intervention," The Oncologist, vol. 8, pp.

5-17, at p. 8, line 19, et seq.

Similar data can be found for other types of cancer recited in claims 27 and 33, such as prostate cancer (Barton, J., et al., Urology (August, 2001) vol. 58, Suppl. 2A, pp. 115 - 122, especially at p. 118, col. 2, line 6).

After the filing of the instant application, the initial results of a Phase I/II clinical trial combining an investigational tyrosine kinase inhibitor, erlotinib, with a monoclonal antibody showed good results in non-small cell lung cancer patients. See Goldman, B., "For Investigational Targeted Drugs, Combination Trials Pose Challenges," J. National Cancer Institute, vol. 95(23) pp. 1744 - 1746 (December 3, 2003) at p. 1744, lst col., lines 40 – 53; see also, "Avastin-Tarceva Combo Provides 'One-Two' Punch Against Lung Cancer," Science Daily (June 7, 2004). However, also subsequent to the time of this application, the Food & Drug Administration (FDA) released a statement that an approved drug, gefitinib [ZD-1839], failed to show an overall survival advantage in a clinical trial wherein patients with non-small cell lung cancer were treated. U.S. Food and Drug Administration, "FDA Statement on Iressa," released December 17, 2004, p. 1, lines 8 - 9.

7. In sum, the state of the prior art at the time of this application was that there was considerable scientific data demonstrating that: (1) the "tyrosine kinase pathway" was involved in certain forms of cancer, (2) inhibition of receptor tyrosine kinases such as "HER-2" and "VEGF" were likely targets for those types of cancer in which overexpression of these RTK's is shown (i.e. renal cell carcinomas and glioma tumors, for example), and (3) and small molecule chemical inhibitors targeting the same pathway (such as SU11248 and PTK787/ZK 222584) were in early phase investigational studies, alone and in combination with monoclonal

antibodies. The preliminary results of clinical studies of tyrosine kinase inhibitors in patients with certain carcinomas, melanomas, and glioma tumors were positive, although some clinical study results published after the time of this application were mixed.

Consequently, even though tyrosine kinase pathways have been identified as one of the five main targets for drug development, as a practical matter their use as therapeutic agents for "treating" a broad range of types of cancer remains unpredictable. As stated in the previous Office Action, the pharmaceutical arts are generally unpredictable, and in *In re Fisher*, the court held that, "in cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." In other words, the more unpredictable an area, the more specific enablement is needed in order to satisfy the statute. In the instant case, it has not yet been established in the art that inhibition of tyrosine kinase activity would be effective, or even desirable, across the broad range of cancer types. Added to the unpredictability of the art itself is the question whether the disclosed *in vitro* tests in AML cells (demonstrating suppression of phosphorylation of Flt-3, VEGFR, and PDEGFR, and suppression of AML cell proliferation by two test compounds of the claimed invention) could be reliably and predictably extrapolated to *in vivo* activity in patients with AML, and whether such activity could be reasonably extrapolated further to encompass other types of cancer, as claimed.

Applicants have provided references wherein tyrosine kinase inhibitors are discussed for treating certain specific types of cancer, particularly breast cancer and lung cancer, in early clinical development trials (Phase I/II/III), providing support for enablement in this instance. However, as noted earlier, subsequent studies yielded mixed results in shrinking certain types of

tumors. See, e.g., U.S. Food and Drug Administration, "FDA Statement on Iressa," released December 17, 2004, p. 1, lines 8 - 9 (regarding failure of a clinical trial of gefitinib to show an overall survival advantage in patients with non-small cell lung cancer). The complexity of cancer continues to make clinical responses difficult to project from *in vitro* data.

An overview of the use of tyrosine kinase inhibitors for cancer patients contemporaneous with the instant application indicated that two of the early tyrosine kinase inhibitors available for clinical treatment, trastuzumab (a monoclonal antibody against HER-2/neu receptor tyrosine kinase), and imatinib (an inhibitor of the platelet-derived growth factor tyrosine kinase), had indeed provided positive results in patients with breast cancer and chronic myeloid leukemia, respectively, but cautioned that extension of these early successes to other types of cancer by inhibiting tyrosine kinase activity raised "new challenges." See Sawyers, C., "Rational therapeutic intervention in cancer: kinases as drug targets," Current Opinion in Genetics & Development (2002) vol. 12, pp. 111-115 at p. 111, lines 29 - 48. The article indicated that the status of the target tissue [tumor] in the host was a significant factor in clinical outcome, adding, "it seems clear that future trials of kinase inhibitors should require measurement of the kinase target in tumor tissue." Id. at p. 113, lines 38 - 40. Dr. Sawyers reflected that even though many tyrosine kinases were known to function as oncogenes in laboratory models, and that these kinases were frequently overexpressed in human cancers, "expression of a particular kinase in a human "tumor does not necessarily mean that kinase is an appropriate drug target . . . a kinase inhibitor will be effective only if it inhibits a target whose function is essential for maintenance of the cancer phenotype." Id. at p. 111, line 47 to p. 112, line 4. Sawyers concluded that "extension of kinase-inhibitor therapy to [other] cancers will require significant advances in our

ability to recognize those cancers that depend on a specific kinase pathway for maintenance and progression." Id. at p. 114, lines 3 - 6. This is another indication that, at the time of this application, the art lacked definite benchmarks by which the therapeutic use of tyrosine kinase inhibitors in cancer patients could be predicted or measured.

8. When considering the claim of treating cancer or growth of a solid tumor in claims 26, 27, 32, and 33 using the compounds of Formula (Ia), given the known clinical studies in the art using tyrosine kinase inhibitors to treat certain types of cancer, the two *in vitro* studies in breast cancer cells disclosed in the Specification, one skilled in the art would require an undue quantity of experimentation to make or use the invention for treating all of the claimed types of cancer; however, it would not require an undue quantity of experimentation for the skilled artisan to use the invention for "treating" certain types of cancer, specifically AML, small cell lung cancer, prostate cancer, gastrointestinal cancer, breast cancer, brain cancer and restenosis, with a reasonable likelihood of success.

After applying the Wands factors and analysis in the previous Office Action and considering the evidence discussed above, it is concluded that claims 26, 27, 32, and 33 remain rejected under 35 U.S.C. 112, 1st paragraph, for failing to disclose sufficient information to enable a person of ordinary skill in the art to use the claimed compounds or compositions of Formula (Ia) for " treating cancer." However, in light of all of the factors analyzed above, there is sufficient disclosure in the Specification to enable treatment of several specific types of cancer, namely AML, small cell lung cancer, prostate cancer, gastrointestinal cancer, breast cancer, brain cancer, and restenosis. Of the specific types of cancer listed in claims 27 and 33, there does not appear to be sufficient disclosure in the Specification for "growth of a solid tumor."

9. Claims 22 and 28 also previously rejected under 35 U.S.C. 112, first paragraph, and 35 U.S.C. 101 as being reach-through claims. In view of Applicants' persuasive arguments, the Examiner withdraws the 35 U.S.C. 101 rejections to the claims, but maintains the rejection under 35 U.S.C. 112, first paragraph, as stated above.

10. Claims 22-24 and 28-30 previously rejected under 35 U.S.C. 112, second paragraph as being indefinite. Applicant states that the invention may be used to treat diseases that can be influenced positively by inhibiting tyrosine kinase but does not provide examples as such. Receptor tyrosine kinase inhibitors are suitable for treating certain proliferative diseases, and are desirable in the treatment of diseases found on page 9 of the specification, such as restenosis, breast cancer, prostate cancer, etc. Without further clarification, however, it is unclear what diseases the Applicants are intending to encompass.

Conclusion

11. In conclusion, claims 22-24, 26-30, 32, and 33 are pending. All claims stand rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Coppins whose telephone number is 571.272.0680. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571.272.0699. The fax phone number for the organization where this application or proceeding is assigned is 571.273.8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Coppins
August 4, 2005

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